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Hot News

Unveiling Long COVID-19 Disease

The clinical spectrum of "Severe Acute Respiratory Syndrome Coronavirus type 2" (SARS-CoV-2) infection is wider than initially thought. The coronavirus does not establish a chronic cellular infection, in contrast with HIV or the hepatitis B virus, that keeps their genomes, respectively, as proviruses integrated within the chromosomes or as episomes (Soriano et al. J Antimicrob Chemother 2014). SARS-CoV-2 replicates within the cellular cytosol and generally only produces self-limited illness. Once the immune response develops, viral clearance occurs (Kato et al. J Infect Chemother 2020). Despite this being the rule, post-coronavirus disease (COVID) complications and reports of persistent infections are of increased concern and are attracting much attention.

Centers for Disease Control and Prevention Researchers have recently proposed a new staging for the natural history of SARS-CoV-2 infection (Datta et al. JAMA 2020). Three phases are distinguished: Acute (active viral replication), post-acute hyperinflammatory (antibody positive after 2 weeks), and late sequelae (i.e., cardiovascular and/or neurological/psychological damage after 4 weeks), as shown in Table 1.

The last two phases represent complications that may occur beyond COVID-19, which strictly applies only to the typical symptomatic acute phase of SARS-CoV-2 infection (fever, cough, breath shortness, anosmia, dysgeusia, diarrhea, nausea/vomiting, etc.). Checking acute phase reactants (fibrinogen, C reactive protein, haptoglobin, complement, etc.) may assist in recognition of the hyper-inflammatory phase that surge as a cytokine storm in some individuals. Beyond that stage, diagnostic procedures become less reliable.

Asymptomatic SARS-CoV-2 Infections

Research early in the pandemic suggested that the rate of asymptomatic infections could be above 80%. However, a recent meta-analysis, which included 13 studies involving 21,708 people, calculated the rate of asymptomatic infections to be 17%. Therefore, more than 80% of infected people may develop symptoms within 1-2 weeks, often mild, vanishing in a couple of days (Byambasuren et al. J. Assoc. Med. Microbiol. Infect. Dis. Can. 2020).

Because most people are symptomatic, concentrating on identifying them will help better tracing of contacts since nearly half of viral transmissions occur during the incubation period (He et al. Nature Medicine 2020; 26: 672). However, scientists are divided about whether asymptomatic infections are acting as a 'silent driver' of the pandemic. The above meta-analysis highlighted that asymptomatic individuals were 42% less likely to transmit the virus than symptomatic people. Although those without symptoms had similar initial viral loads – the number of viral particles present in a throat swab – when compared with people with symptoms, asymptomatic persons seem to clear the virus faster and are infectious for a shorter period. Their immune systems might be able to neutralize the virus more rapidly. Even so, asymptomatic individuals should continue to use measures that reduce viral spread, such as social distancing and wearing a mask.

Persistent Symptoms and COVID-19 Complications

Although complete recovery is the rule after experiencing acute SARS-CoV-2 infection, one in 20 people with COVID-19 seems to experience symptoms for 8 weeks or more. These late sequelae are known as 'long COVID' (Editorial. Nature 2020).

Long COVID must be differentiated from other well-defined post-COVID complications, mostly grouped within three categories:

1. Residual failure at organs other than the lungs following damage during acute coronavirus infection. This is the case for kidney insufficiency after acute renal involvement or heart insufficiency after myocarditis.
2. Long-term disabilities after prolonged stages at the intensive care unit during a severe COVID-19 episode. As with other serious illnesses, time to recovery after weeks of admission at ICU may last for months and require rehabilitation and physiotherapeutic interventions.
3. Persistent coronavirus replication in patients under immunosuppression. Anecdotal cases of SARS-CoV-2

Table 1. CDC staging for SARS-CoV-2 infection (COVID-19)

	Acute	Hyperinflammatory	Long COVID
Time frame	< 2 weeks	2 - 4 weeks	> 4 weeks
Pathogenesis	Viral replication	Immune response	?
Symptoms	Fever, headache, Respiratory (cough, dyspnea) GI (nausea, diarrhea)	Cardiovascular, Neurological, Dermatological, Musculoskeletal	Fatigue, Psychological
Diagnosis	PCR and antigen testing	Antibody testing	?

replication for 3-6 months have been reported accompanied by fluctuating clinical symptoms of fever, cough, dyspnea, etc., (Chi et al. N Engl J Med 2020; and Helleberg et al. J Infect Dis 2020).

The last observation reminds what was described one decade ago with hepatitis E virus, another RNA virus that typically causes self-limited infection. However, unexpectedly cases of chronic hepatitis and cirrhosis due to HEV began to be confirmed in liver transplant recipients, in clear association with immunosuppressants (Kamar et al. N Engl J Med 2008).

The True "Long COVID"

Beyond the prior three situations, what we really mean with "long COVID" refers more properly to post-viral fatigue or chronic fatigue syndrome (Komaroff et al. JAMA 2019), also known as myalgic encephalomyelitis. This is a not well-defined illness that has been associated with some infectious agents, including herpesviruses such as Epstein-Barr or cytomegalovirus, that establish chronic infections, with periods of latency and reactivation. These patients complain fatigue with premature physical exhaustion, sleep disturbances, mood abnormalities with depression predominantly, difficulties in concentration and memory loss, etc. Many people say that it is like experiencing suddenly accelerated aging.

In the United Kingdom, data from 4182 individuals that tested positive for SARS-CoV-2 through swab PCR exam suggest that while most people with COVID-19 reported being back to normal within 11 days, around one in seven (13.3%) had COVID-19 symptoms lasting for at least 4 weeks, with around one in 20 (4.5%) staying ill for 8 weeks and one in 50 (2.3%) suffering for longer than 12 weeks (Sudre et al. medRxiv 2020).

The King's College study identified two main symptom groupings in long COVID. One was dominated by respiratory symptoms such as cough and shortness of breath, as well as fatigue and headaches. The second form was clearly multi-systemic, affecting many parts of the body, including the brain, gut, and heart. Long COVID sufferers more commonly reported heart symptoms such as palpitations or fast heartbeat, as well as pins and needles or numbness, and problems concentrating ("brain fog").

Overall, long COVID affects around 10% of SARS-CoV-2 infected adults < 50 years old, rising to 22% in those over 70 s. Weight plays a role, with people developing long COVID having a higher average body mass index than the rest. Finally, women are 50% more likely to suffer from long COVID than men (14.5% compared with 9.5%).

From other human viruses that establish chronic infection, such as HIV or hepatitis B or C viruses, we known that chronic inflammatory phenomena and persistent immune activation seem to result from residual viral replication, occasionally at certain tissues and/or cell reservoirs. It contributes to dysregulation of metabolic pathways and accelerated aging processes. However, this pathophysiologic mechanism would be difficult to accept for coronaviruses since they generally lead to self-limited infections. However, the unique cytokine storm that occurs in a subset of COVID-19 patients after 2 weeks of infection (Mehta et al. Lancet 2020) might disrupt the mechanisms that suppress the expression of endogenous viruses and/or epigenetic changes that regulate cell turnover. Only the long-term follow-up of large series of patients that have experienced SARS-CoV-2 infection would provide further insights into the pathogenesis of long COVID.

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